REMARKS

This amendment is in response to the Non-Office Action mailed July 31, 2006.

Claims 1-9, 11-14, and 24-25 are pending. Claims 15-17 and 19-23 have been withdrawn by the Examiner. Claim 10 has been withdrawn by the Applicant. Claim 18 has been cancelled without prejudice. The specification has been amended discussed below to correct typographical errors. No new matter has been added by the amendments.

A Petition for a Three (3) Month Extension of Time under 37 C.F.R. §1.136(a) is enclosed herewith along with a check for $1020.00 to cover the large entity fee as per 37 C.F.R. §1.17(a)(3).

SPECIFICATION AMENDMENT

Applicant notes that the relevant portion of page 42 of the specification was previously amended in the Response filed on February 10, 2006. Nevertheless, in response to the Examiner's objection, the specification has been amended herewith on page 42 to correct typographical errors. Namely, please replace page 42, lines 9-23 with the above replacement section, inserting "SEQ. ID NO: 5." No new matter has been added by the amendments. Withdrawal of the objection is respectfully requested.

§112 REJECTIONS

Claim 25 was rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant respectfully disagrees with the rejection.

Namely, it is respectfully asserted that the referenced amino acid sequence in Fueyo most likely contains typographical errors. Figure 1A on page 3 of Fueyo depicts the relevant sequence of stretch of nucleotides that is deleted. As can be seen in FIG. 1A of Fueyo, this stretch ends with the sequence "GGCTTT". Note that a "GGC" codon encodes a glycine (G) and not, as Fueyo incorrectly states, a cysteine (C). Applicant submits herewith for the Examiner's ready reference an RNA codon table showing the 64 codons and the amino acid each codon codes for. The direction is 5' to 3'. (*See* Table 1 below). The "GGCTTT" nucleotide sequence presented by Fueyo is also the one that is entered in the database for Ad5.

Table 1: RNA codon table

		2nd base			
		U	C	A	G
1st base	U	UUU (Phe/F)Phenylalanine UUC (Phe/F)Phenylalanine UUA (Leu/L)Leucine UUG (Leu/L)Leucine	UCU (Ser/S)Serine UCC (Ser/S)Serine UCA (Ser/S)Serine UCG (Ser/S)Serine	UAU (Tyr/Y)Tyrosine UAC (Tyr/Y)Tyrosine UAA Ochre *(Stop)* UAG Amber *(Stop)*	UGU (Cys/C)Cysteine UGC (Cys/C)Cysteine UGA Opal *(Stop)* UGG (Trp/W)Tryptophan
	C	CUU (Leu/L)Leucine CUC (Leu/L)Leucine CUA (Leu/L)Leucine CUG (Leu/L)Leucine	CCU (Pro/P)Proline CCC (Pro/P)Proline CCA (Pro/P)Proline CCG (Pro/P)Proline	CAU (His/H)Histidine CAC (His/H)Histidine CAA (Gln/Q)Glutamine CAG (Gln/Q)Glutamine	CGU (Arg/R)Arginine CGC (Arg/R)Arginine CGA (Arg/R)Arginine CGG (Arg/R)Arginine
	A	AUU (Ile/I)Isoleucine AUC (Ile/I)Isoleucine AUA (Ile/I)Isoleucine AUG (Met/M)Methionine, *Start*[1]	ACU(Thr/T)Threonine ACC (Thr/T)Threonine ACA (Thr/T)Threonine ACG (Thr/T)Threonine	AAU(Asn/N)Asparagine AAC (Asn/N)Asparagine AAA (Lys/K)Lysine AAG (Lys/K)Lysine	AGU (Ser/S)Serine AGC (Ser/S)Serine AGA (Arg/R)Arginine AGG (Arg/R)Arginine
	G	GUU (Val/V)Valine GUC (Val/V)Valine GUA (ValIV)Valine GUG (Val/V)Valine	GCU (Ala/A)Alanine GCC (Ala/A)Alanine GCA (Ala/A)Alanine GCG (Ala/A)Alanine	GAU (Asp/D)Aspartic acid GAC (Asp/D)Aspartic acid GAA (Glu/E)Glutamic acid GAG (Glu/E)Glutamic acid	GGU (Gly/G)Glycine GGC (Gly/G)Glycine GGA (Gly/G)Glycine GGG (Gly/G)Glycine

Claims 5, 6 and 8 were rejected under 35 U.S.C. §112, first paragraph as failing to comply with the enablement requirement. Applicant respectfully disagrees with the Examiner's assertion that in view of the state of the art, one skilled in the art could not practice the invention without undue experimentation as it is broadly claimed.

The examiner is kindly referred to Figure 7 of the present application and the reference thereto on page 20, line 31 to page 21, line 3 of the Substitute specification. Namely, Figure 7 presents the results of an experiment using conditionally replicating adenoviruses. The viruses and the generation thereof are described in Example 1 of the present application (pages 41-43 of the Substitute specification). The virus AdΔ55K-p53 includes an E1B-55kDa protein deletion and a coding region for p53. The virus AdΔ24-p53 contains an E1A CR2-mutation and a coding region for p53.

Figure 7 shows culture dishes of A549, SaOs-2 and U373MG cells that had been infected with the indicated viruses 14 days before. The amount of virus used for the infection is represented as MOI, i.e. multiplicity of infection. This number is the ratio of the number of infectious viruses measured as plaque forming units (pfu) versus the number of cells used. An MOI of 1 indicates that the number of infectious virus used for the infection equals the amount of cells. An MOI of 10 indicates that ratio of viruses to cells was 10, etc.

It can be seen that cells are present in the control cultures that were not infected with the virus (dishes marked "control"). The three different cell lines have different sensitivities to the viruses used for the infection. However, in all cases the E1B-55k positive virus (AdΔ24-p53) kills the cells at a lower MOI than the E1B-55k negative virus (AdΔ55-p53). Thus, less virus is needed to kill the cells when a virus is used that

contains a coding region for E1B-55k. This means that the virus kills cells more rapidly in the presence of E1B-55k than in the absence thereof. The oncolytic activity of a virus of the invention is thus enhanced in the presence of E1B-55k. Accordingly, Applicant respectfully submits that claims 5, 6 and 8 are therefore enabled.

It is therefore respectfully requested that all the §112 rejections be withdrawn.

§102 REJECTIONS

Claims 1, 2, 9, 24 and 25 were rejected under 35 U.S.C. §102(b) as being anticipated by Fueyo et al. (Oncogene.2000.19:2-12) hereinafter Fueyo, as evidenced by Nevins (Human Molecular Genetics.2001.10(7):699-703). Applicant respectfully disagrees.

Fueyo provides cells with an adenovirus having an E1A Δ24 protein that is no longer capable of binding Rb (page 2, lines 1-10).

It is respectfully submitted that lytic activity does not act via Rb.

This is evident from the fact that cells in which the Rb pathway are restored are **not** killed by the virus (see page 7, first paragraph of the "Discussion" in Fueyo). Thus, a functional Rb-pathway does not allow the virus to kill the cells. Furthermore, the cells are provided with an E1A-Δ24 protein that cannot bind to Rb. Thus any effect displayed by the virus cannot be governed by the Rb-pathway as the protein cannot interact with Rb. The oncolytic effect of the Fueyo Δ24 virus can therefore not be mediated by the interaction of E1A with Rb. The Δ24 protein does not facilitate this interaction.

The comment in Fueyo on page 7, *Treatment with Δ24*, that is referred to by the Examiner on page 9 of the Office Action, must be seen in the above-mentioned context. Fueyo's remark exemplifies Fueyo's opinion that the virus kills, irrespective of the status

of p53 in the cells *(see* last 6 lines of "*Treatment with Δ24*" in the left column of page 7 of Fueyo). The presence of p53 independent apoptosis is well known and is also referred to by Nevins. Nevins mentions that E2F1 (a factor controlled by Rb), can induce apoptosis independent of P53 (*see* Nevins, page 700, first paragraph of the right hand column).

Neither Fueyo nor Nevins disclose or suggest at least a replication competent recombinant adenovirus comprising in the genome a coding sequence of at least one restoring factor functional in restoring the p53 apoptosis pathway in target cells, essentially as claimed in claim 1. Since the E1A Δ24 protein in the Fueyo virus does not interact with Rb, it cannot restore a pathway via this interaction. If an apoptosis pathway is present in these cells it is functional irrespective of the E1A Δ24 protein.

It is therefore submitted that the features of claim 1 are not anticipated by nor inherently present in Fueyo as evidenced by Nevins. Claims 2, 9, 24 and 25 depend from and include the limitations of claim 1, and are therefore believed to be patentable and nonobvious for at least the reasons stated above for claim 1.

Claims 1-7, 14 and 24 were rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 6,638,762 to Chang et al. (hereinafter Chang) as evidenced by Bressac et al.(PNAS.1990.87:1973-1977) hereinafter Bressac, and further evidenced by Moore et al. (PNAS.1996.p.11295-11301), hereinafter Moore. Applicant respectfully disagrees.

It is respectfully submitted that Chang does not disclose at least a replication competent adenovirus comprising in the genome a coding sequence of at least one restoring factor functional in restoring the p53 apoptosis pathway in target cells,

essentially as claimed in claim 1. Such a coding sequence is neither mentioned nor suggested by Chang. The Examiner refers to infection of Hep3B cells with adenovirus Av15E1aTk04i and states that this infection inherently anticipates the claims mentioned herein above.

To be anticipated under 35 U.S.C. §102, the reference(s) "must teach every aspect of the claimed invention either explicitly or impliedly. Any feature not directly taught must be inherently present." *See* M.P.E.P. 706.02.

The adenovirus Av15E1aTk04i contains the TIC gene as the cytotoxic gene. This gene is not involved in a p53 apoptosis pathway and is also not functional in restoring a p53 apoptosis pathway. The example referred to by the Examiner can therefore not be an inherent or implied disclosure of the recitation of the present claim 1, as claim 1 requires that the adenovirus comprises in the genome a coding sequence of at least one restoring factor functional in restoring the p53 apoptosis pathway in target cells. It is further noted that Chang mentions only that the virus replicates in the Hep3B cells. There is no disclosure, suggestion or mention whatsoever of at least oncolytic activity, apoptosis or enhanced replication.

Furthermore, there are many ways to kill a cell. The present invention is directed toward killing through providing a cell with a replication competent adenovirus comprising a coding sequence of at least one restoring factor functional in restoring the p53 apoptosis pathway in target cells. Infection of a cell deficient in p53 and finding that an adenovirus replicates therein is not the same as providing an adenovirus comprising a coding sequence of at least one restoring factor functional in restoring the p53 apoptosis pathway in target cells. Instead, Chang teaches and contemplates completely different

methods for killing target cells. E.g., Chang mentions various toxic effects (see Chang, column 22, lines 19-46) none of which are directed towards or suggest restoring the p53 apoptosis pathway in target cells.

It is therefore submitted that the features of claim 1 are not anticipated by nor inherently present in Chang. Claims 2-7, 9, 14 and 24-25 depend from and include the limitations of claim 1, and are thus believed to be patentable and nonobvious for at least the reasons given above for claim 1.

Withdrawal of all the §102 rejections is respectfully requested.

§103 REJECTIONS

Claims 1 and 11-13 were rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (Cancer Research.Oct 15, 2000.60.p.5895-5901), hereinafter Lin, in view of Chang et al. as mentioned above in the 35 U.S.C. 102 rejection (hereinafter Chang). Applicant respectfully disagrees.

It is respectfully asserted that an artisan of ordinary skill in the art would not use the mutated P53 gene in Lin to construct a replication competent adenovirus comprising in the genome a coding sequence of at least one restoring factor functional in restoring the p53 apoptosis pathway in target cells, essentially as claimed in claim 1. Note that P53 functions differently in a cell infected with a replication competent recombinant adenovirus. Reference is made to Figure 1 of the present specification, in which the cell viability (expressed as WST- 1 conversion units) of cells of various origins is presented in relation to the days after infection with 4 different (combinations) of adenoviruses.

The cells are infected with replication defective virus (GFP or p53 containing

viruses (AdGFP and Adp53 respectively). As the adenovirus vectors are replication defective they can only replicate when the deficiency is complemented in trans by the target cell. The cell viability of cultures of cells infected with these replication defective viruses is compared with the cell viability in a comparative experiment wherein the same viruses are used to infect the cells but now in the presence of an adenovirus that expresses the E1 region (AdE1+Luc). In this situation, the replication defective GFP and p53 adenoviruses are "rescued" and also able to replicate in the target cells.

It can be seen in FIG. 1 of the specification that the replication defective GFP and p53 viruses do not differ very much in the effect on cell viability on the infected cells. On the other hand, the viruses do have a significantly different effect in cells that replicate the adenovirus.

Lin observes an anti-proliferative effect of a modified p53 (*see* abstract and discussion) and suggests therewith that the cancer cells are provided with normal growth regulatory control, that was absent in the untreated cancer cells. It is noted that this activity is completely different from the activity of the claimed viruses of the present invention. The adenoviruses of the present invention comprise an oncolytic effect that is based on a different mechanism than the anti-proliferative effect in Lin. Lin in fact teaches *away* from the present invention. Infection of cancer cells with the virus of Lin induces growth arrest. This is wholly opposite from the effect that is desired in the present invention. Adenovirus needs replication of the cells, or at least the S-phase thereof, for its own replication (*see* e.g., page 6, lines 26-35 of the specification). One of ordinary skill in the art therefore knows that the anti-proliferative effect observed in Lin is not compatible with a replication competent adenovirus.

Furthermore, Lin does not teach or suggest the enhanced oncolytic effect of the viruses of the present invention.

Figure 2 of the present application depicts the yield of recombinant adenovirus viruses. The figure compares the yield of GFP viruses versus the yield of p53 viruses. It can be seen that the p53 viruses replicate significantly faster than the GFP viruses. This feature at least contributes to the observed oncolytic effect of the viruses of the present invention. Neither Lin nor Chang, either alone or in any combination, teach or suggest this property.

It is therefore respectfully and strongly asserted that the skilled artisan would not combine Lin with Chang. Even assuming, *arguendo*, that they could be combined, such combination would fail to disclose or suggest the present invention as claimed in claim 1. Namely, as discussed above, Chang does not teach, suggest or mention the oncolytic and replication enhancing features of a virus of the present invention.

It is therefore submitted that the features of claim 1 are patentable and nonobvious over Lin in view of Chang. Claims 11-13 depend from and include the limitations of claim 1, and are thus believed to be patentable and nonobvious for at least the reasons given above for claim 1.

Withdrawal of all the §103 rejections is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that claims 1-9, 11-14, and 24-25 are patentable and nonobvious over the cited references. Consequently, the Applicants respectfully request reconsideration and withdrawal of the objections and rejections and allowance of the application. Such early and favorable action is earnestly solicited.

A Petition for a Three (3) Month Extension of time and corresponding large entity fee for same is enclosed herewith. It is believed that no additional fees or charges are currently due. However, in the event that any additional fees or charges are required at this time in connection with the application, they may be charged to applicant's representatives Deposit Account No. 50-1433.

Respectfully submitted,
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